Vitamin D Deficiency

Background
1. Definitions
   - Vitamin D is a fat-soluble vitamin
   - Vitamin D deficiency is measured by low circulating levels of 25-OH vitamin D in the serum

Pathophysiology
1. Absorption and metabolism
   - 2 main sources of Vitamin D
     - Vitamin D3 (cholecalciferol) - activated in skin by UV light
     - Vitamin D2 (ergocalciferol) - ingested form
   - Vitamin D is hydroxylated in liver to 25-OH Vitamin D (calcidiol)
     - Best serum marker of vitamin D sufficiency
   - Calcidiol is hydroxylated in kidney to 1,25-OH Vitamin D (calcitriol)
     - Most biologically active form
2. Normal physiology
   - Vitamin D
     - Facilitates intestinal absorption of calcium and phosphate
     - Acts mainly in upper small intestine
     - Enhances renal reabsorption of phosphate
     - Aids in mineralization of bone
     - Plays a major part in homeostasis of calcium and phosphate
   - Calcium metabolism
     - Ionized calcium in ECF is maintained in a very narrow range
     - Low serum calcium stimulates PTH release from parathyroid glands
     - PTH encourages calcium resorption from bone and decreases calcium excretion from kidneys
     - PTH stimulates production of 1,25-OH Vitamin D in the kidney, which in turn increases intestinal calcium absorption
     - Elevated serum calcium suppresses PTH and Vitamin D production
3. Pathology of disease
   - Decreased vitamin D leads to
     - Reduced absorption of calcium if Vitamin D deficiency is moderate - severe
     - Hypocalcemia may lead to decreased bone mineralization, muscle cramps, spasm, tetany, seizures, confusion, encephalopathy, papilledema, and QT prolongation
     - Stimulated release of PTH
     - Stimulates resorption of calcium from bone
     - Decreased resorption of phosphate in the kidney
   - Elevated vitamin D levels
     - Rare, seen mostly due to over-supplementation
     - May lead to hypercalcemia and hypercalciuria
4. Incidence and prevalence
   - Certain patient groups at high risk for Vitamin D deficiency
   - Children
     - Among 618 Asian children in UK, 27% were vitamin D deficient
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Elderly
- In homebound elderly, 54% prevalence in community dwellers and 38% in nursing home residents

Hospitalized patients
- 57% of patients on a general medical service
- Subgroup of patients with no known risk factors had 42% prevalence
- Women treated for osteoporosis
- 52% of community-dwelling women were also Vitamin D deficient
- Chronic renal disease
- 28-58% Vit D deficiency in patients with decreased GFR
- Gastrointestinal disease
- Healthy adults in winter
- 36% of healthy adults residing in Boston demonstrated Vitamin D deficiency at the end of winter as opposed to only 4% at the end of summer

5. Risk factors
- Inadequate sun exposure
  - Infants
  - Decreased sun exposure
  - Breast milk is poor source of Vitamin D
  - Formula supplementation only adequate if >1 L consumed daily
  - Persons residing at northern latitudes
  - Elderly
  - Indoor confinement
  - Skin of those older than 70 does not convert vitamin D effectively
  - Poor vitamin D intake
- Inadequate dietary intake
  - Vitamin D found naturally in fatty fish, cod liver oil, and small amounts in eggs, butter, cheese
  - Commercial milk and cereals fortified with Vit D, but amounts may be inconsistent
- Malabsorption
  - Fat malabsorption, steatorrhea
  - Celiac disease, cystic fibrosis
- 5 hydroxylase deficiency
- Increased catabolism
  - Vitamin D catabolized in liver by p450 system
  - Catabolism accelerated by phenytoin, phenobarbital, alcohol
- End-organ resistance
  - Hereditary vitamin D resistant rickets

6. Morbidity/ mortality
- Inadequate treatment can lead to:
  - Osteomalacia (rickets in children)
  - Associated hypocalcemia may result in osteoporosis, fractures, seizures
  - Some evidence of increased all-cause mortality among elderly
Diagnostics
1. History
   - Dietary intake – cod liver oil, fatty fish, egg yolks, cheese, supplemented milk and cereals
   - Sun exposure / sunscreen use
   - Mostly asymptomatic
   - Moderate to severe deficiency may result in non-specific musculoskeletal pain
     - Has been identified in patients with no known risk factors for Vitamin D deficiency
     - Vitamin D replacement may not improve pain symptoms
2. Physical exam
   - No findings specific to vitamin D deficiency
3. Diagnostic testing - Decreased serum 25-OH vitamin D
   - Laboratory evaluation: assays may vary, making exact measures difficult to define
     - Optimal levels 30-40 ng/ml (75-100 nmol/L)
     - Mild vitamin D deficiency 10-20 ng/ml (25-50 nmol/L)
     - Increased PTH production and bone turnover
     - Moderate vitamin D deficiency 5-10 ng/ml (12.5-25 nmol/L)
     - High bone turnover, reduced bone density, increased risk hip fracture
     - Severe vitamin D deficiency <5 ng/ml (<12.5 nmol/L)
     - Osteomalacia
   - Poor indicators of vitamin D status:
     - Calcium, phosphate, alkaline phosphatase, PTH
4. Diagnostic imaging
   - Incidental finding on radiograph
   - Osteopenia/osteoporosis may suggest Vitamin D deficiency
   - Rickets/osteomalacia may be seen on X-ray

Differential Diagnoses
1. Vitamin D deficiency is established by serum testing
2. See Risk factors for review of underlying causes

Therapeutics
1. Vitamin D replacement
   - Cholecalciferol (Vitamin D3) is preferred supplement (SOR:2C)
   - Severe deficiency - Treatment recommended (SOR:1A)
     - Treat with vitamin D 50,000 IU once per week for 6-8 weeks
   - Mild to moderate deficiency - Treatment recommended (SOR:2B)
     - Treat with vitamin D 800 - 1000 units / day and check levels in 3 months
     - May need higher doses if inadequate response
   - Continue Vitamin D intake of 800 - 1000 units/day to maintain adequate 25 OH Vit D
   - Vitamin D metabolites calcidiol or calcitriol may be required in patients with liver or renal disease
     - Calcidiol not available in the US
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- Calcitriol used mainly in patients with chronic renal failure
  - Check levels 3 months after initiating treatment

2. Precautions
  - Vitamin D toxicity has been noted at levels as low as 88 ng/ml
    - Hypercalcemia
    - Hypercalciuria
  - Calcitriol has rapid onset and half life of 6 hr
    - High incidence of hypercalcemia and patients should be monitored closely

Prognosis
1. No sequelae with proper treatment

Prevention & Screening
1. Prevention
  - Exposure to ultraviolet light of limited use as risks may outweigh benefits
  - Oral consumption of vitamin D 800-1000 units/day for adults (SOR:2B)
  - Infants
    - 400 IU of Vitamin D daily beginning in 1st few days of life for all breast and formula fed infants
    - Formula fed infants will receive adequate Vitamin D if they consume >1 L of Vit D supplemented formula / day
  - Pregnancy and lactation
    - No current recommendation, but maternal vitamin D deficiency is a known risk factor for infant vitamin D deficiency
    - It is therefore reasonable to assess Vitamin D intake in pregnant and lactating mothers

2. Screening
  - No recommendation for routine screening (SOR:2C)

Patient Education

References
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